0022-3565/85/2341-0153$02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 234, No. 1

Printed in U.S.A.

Nicotine Renal Excretion Rate Influences Nicotine Intake during Cigarette Smoking[1]

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Accepted for publication April 8, 1985

ABSTRACT

We examined the hypothesis that rate of elimination of nicotine affects nicotine intake during cigarette smoking. Elimination rate was altered by administering ammonium chloride or sodium bicarbonate throughout the day. Nicotine intake during unrestricted cigarette smoking was measured using metabolic clearance data obtained after i.v. nicotine infusion together with blood and urinary nicotine concentrations measured during 24-hr periods of cigarette smoking. Compared with placebo treatment (urine pH 5.6), urinary acidification (pH 4.5) increased (208%) renal clearance and, to a lesser extent (41%), total clearance and increased (by 7.2 mg) daily urinary excretion of nicotine. Urinary alkalinization (pH 6.7) resulted in a decrease (78%) in renal clearance with a small decrease (3.7 mg) in daily nicotine excretion. Average blood nicotine concentrations were similar in placebo and bicarbonate treatment conditions, but were 15% lower during acid loading. Daily intake of nicotine was 18% greater during acid loading. The compensatory increase in nicotine consumption was only partial, replacing about half the excess urinary nicotine loss. This is the first direct demonstration that rate of elimination can influence self-determined drug consumption in humans.

If smokers regulate nicotine intake to maintain a particular body level, nicotine elimination rate should be an important determinant of smoking behavior. The rate of renal elimination of nicotine is influenced by urinary pH (Beckett *et al.*, 1965; Feyerabend and Russell, 1978; Rosenberg *et al.*, 1980). Urinary acidification increases nicotine self-administration in rats (Lang, 1980) and cigarette consumption in humans (Schachter *et al.*, 1977). Fluctuations in urinary pH, perhaps related to stress, are thought to be a determinant of stress-related increases in cigarette consumption (Schachter, 1978). Therapy with alkali has been suggested as an adjunct for treatments to stop smoking (Fix *et al.*, 1983).

Only one study examined how well nicotine levels are regulated when there is a change in rate of elimination. Plasma nicotine concentrations in one person smoking cigarettes or chewing nicotine gum on a regular schedule for 8 hr under acid or alkaline urine conditions were higher in alkaline *vs.* acidic urine conditions (Feyerabend and Russell, 1978). However, blood levels of a drug are determined by both intake and clearance. Inasmuch as Feyerabend and Russell (1978) did not measure clearance, they could not determine whether rate of elimination affected intake of nicotine.

We measured the influence of urinary acidification and alkalinization on blood nicotine levels and on intake of nicotine during daily smoking. Daily intake of nicotine was estimated using metabolic clearance data obtained after i.v. infusion together with blood and urine nicotine concentrations measured during 24-hr periods of smoking (Benowitz and Jacob, 1984).

The following questions were addressed: Does a smoker compensate for accelerated or reduced rate of elimination of nicotine from the body? If there is compensation, how complete is it and how much of the compensation is accomplished by consuming more or less nicotine per cigarette?

Methods

Eleven healthy paid volunteers, eight men and three women, 28 to 55 years of age (mean 38 ± 10, S.D.), were studied. All were habitual cigarette smokers whose average daily consumption was 48 ± 10 cigarettes (range, 30–60) and who had smoked for an average of 21 ± 12 years (range, 6–40 years). Six smoked filtered and five smoked nonfiltered cigarettes. Federal Trade Commission yields for their usual cigarette brands averaged 18.7 ± 4.3 mg of tar, 1.3 ± 0.2 mg of nicotine and 14.9 ± 1.5 mg of CO.

Subjects were hospitalized on a clinical research ward for 14 days (eight subjects) or 8 days (three subjects). Subjects ate a normal diet except that caffeine-containing beverages and alcohol use were prohibited. On the 2nd hospital day, after overnight abstinence from smoking, nicotine was infused i.v. to determine metabolic clearance (Benowitz and Jacob, 1984). Eight subjects were then studied in four 3-day experimental blocks during which they could smoke as they wished. In the first block, no medication was given (base line). During the next three blocks, capsules were given every 4 hr while awake. Capsules contained lactose (the placebo), ammonium chloride (2 g) or sodium bicarbonate (2 g). The sequence of treatments was balanced

Received for publication December 28, 1984.
[1] This work was supported in part by U.S. Public Health Service Grants CA32389, DA02277 and DA01696. These studies were carried out in part in the General Clinical Research Center (RR-00083) with support of the Division of Research Resources, National Institutes of Health.

using 3 × 3 Latin squares (less one sequence). Three subjects were studied only during ammonium chloride and sodium bicarbonate periods with no base-line or placebo periods. The treatment sequence was alternated in successive subjects.

All cigarette butts were weighed. Grams of tobacco consumed daily were estimated by subtracting the butt weight from the weight of a comparable number of unburned cigarettes. Urine was collected every 24 hr to measure daily nicotine excretion. Urine pH was recorded at every voiding. On the last day of each study block, a circadian blood sampling study was performed (Benowitz and Jacob, 1984). In five subjects, on the 2nd day of each study block arterialized venous blood was obtained for measurement of pCO_2 and pH from which plasma bicarbonate was calculated (Forster *et al.*, 1972).

Because not all subjects participated in all four experimental blocks, comparisons were made for treatment blocks with equal numbers of subjects by paired *t* test. For example, ammonium chloride or sodium bicarbonate treatment values were compared to placebo for eight subjects, whereas ammonium chloride and sodium bicarbonate could be compared to each other in 11.

Results

Compared with base-line, placebo treatment had no significant effect on pH, renal clearance or nicotine excretion. Compared with placebo, ammonium chloride treatment reduced urinary pH (from an average of 5.6–4.5) and increased nicotine renal clearance (from 182–562 ml/min) and daily excretion of nicotine (4.6–11.8 mg) (see table 1; fig. 1). Sodium bicarbonate increased urinary pH to 6.7. This decreased renal nicotine clearance to 39 ml/min and daily nicotine excretion to 0.9 mg.

Arterialized venous blood gases were measured in five subjects during ammonium chloride and sodium bicarbonate administration. Plasma bicarbonate concentration was significantly lower during ammonium chloride (20.6 ± 3.3 mEq/l) compared with sodium bicarbonate (22.2 ± 1.9 mEq/l); similar changes were observed for pCO_2 (35.3 ± 3.4 torr *vs.* 37.6 ± 3.4 torr), whereas pH was not affected.

Subjects smoked a similar number of cigarettes, burned the same weight of tobacco and consumed the same amount of nicotine each day in base-line and placebo treatment conditions (table 1). Thus, hospitalization *per se* did not affect nicotine intake. In both acid and alkali treatment conditions, smokers tended to smoke more cigarettes and consume more tobacco. Average nicotine blood levels (estimated as area under the blood nicotine concentration-time curve during 24 hr) were similar in placebo and alkali treatment conditions, but were 15% lower in the acid loading condition (fig. 2).

Daily nicotine intake was 18% greater during the acid compared with the alkali loading condition. On average, smokers consumed more nicotine per cigarette during acid compared with alkali loading but not when compared with base line or placebo. Despite the greater consumption of nicotine in the acid treatment condition, average carbon monoxide level (area under the blood carboxyhemoglobin concentration-time curve during 24 hr) was lower during acid treatment.

Discussion

Acidification increased urinary nicotine clearance by 200%. Alkalinization decreased clearance by 78% of placebo treatment values. Total clearance (renal plus metabolic) increased 41% and decreased 1%, respectively. On average, half the increased urinary excretion was compensated for by increased nicotine intake. Compensation was incomplete based on the observation that average nicotine blood levels declined by 15% in the acid loading condition. On an average, smokers smoked the same numbers of cigarettes in acid and alkaline conditions, indicating that differences in nicotine intake were achieved by changes in smoking behavior, perhaps alterations in puff and inhalation volumes or number (Herning *et al.*, 1983). Carbon monoxide levels were not useful as an indicator of nicotine intake in this study. During ammonium chloride treatment, the metabolic acidosis produced hyperventilation. Carbon monoxide clearance is known to be dependent on ventilatory rate (Lawther, 1975). Therefore, hyperventilation produced by ammonium chloride would be expected to lower carbon monoxide levels despite increased nicotine and tobacco smoke intake.

Our data are consistent with animal studies showing compensatory increase in nicotine consumption (Lang, 1980) and studies in people showing increased cigarette consumption (Schachter *et al.*, 1977) when urinary nicotine loss is increased by acidification. Our observation that compensation for increased nicotine loss due to urine acidification is incomplete is similar to that observed in one subject studied by Feyerabend and Russell (1978). Likewise, only partial compensation occurs when switching smokers from higher to lower yield cigarettes (Benowitz *et al.*, 1982; Russell *et al.*, 1975).

Caution should be exercised in applying the findings to usual smoking situations. We performed our studies under conditions of extreme urinary acidification or alkalinization, so that the changes in renal clearance would be maximized. Even with extreme differences in urinary pH, differences in overall nico-

TABLE 1

Influence of urinary pH on rate of elimination, body levels and intake of nicotine during unrestricted cigarette smoking

Data are expressed as mean ± S.D. AUC_{nic}, area under the blood nicotine concentration-time curve during 24 hr; AUC_{COHb}, area under the blood carboxyhemoglobin concentration-time curve during 24 hr.

Treatment	Urine pH	Nicotine Excretion	Renal Clearance	Total Clearance	Cigarettes/ Day	Tobacco/ Day	AUC_{nic}	Nicotine Intake	Nicotine Intake/ Cigarette	AUC_{COHb}
		mg/day	*ml/min*	*ml/min*		*g*	*ng·ml⁻¹·hr*	*mg/24 hr*	*mg*	*%·hr*
Base line (*N* = 8)	5.8	3.1	102	1153	39	42.6	514	37.7	0.90	192
	±0.3	±1.6	±41	±383	±11	±16.5	±231	±22.9	±0.39	±96
Placebo (*N* = 8)	5.6	4.6	182	1240	39	42.2	455	36.6	0.89	182
	±0.6	±2.8	±103	±391	±11	±17.0	±182	±21.7	±0.39	±65
Ammonium chloride (*N* = 11)	4.5[a,b]	11.8[a,b]	562[a,b]	1751[a,b]	44	46.9	409[a]	43.4[a]	0.92[a]	154[a]
	±0.4	±4.3	±210	±235	±13	±18.1	±252	±30.4	±0.43	±63
Sodium bicarbonate (*N* = 11)	6.7[b]	0.9[b]	39[b]	1226	43	46.3	479	36.8	0.82	175
	±0.3	±1.0	±58	±368	±13	±18.9	±215	±26.5	±0.41	±72

[a] Ammonium chloride *vs.* sodium bicarbonate, $P < .05$.
[b] Ammonium chloride or sodium bicarbonate *vs.* placebo, $P < .05$.

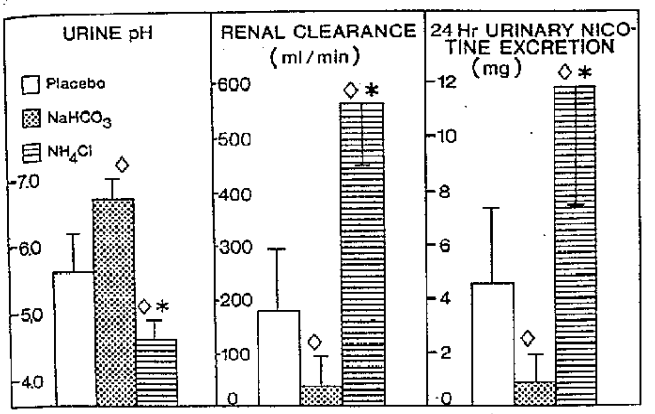

Fig. 1. Influence of urine pH on renal clearance of nicotine and 24-hr urinary excretion. ◇, significant differences compared to placebo. *, significant differences, $NaHCO_3$ *vs.* NH_4Cl treatment.

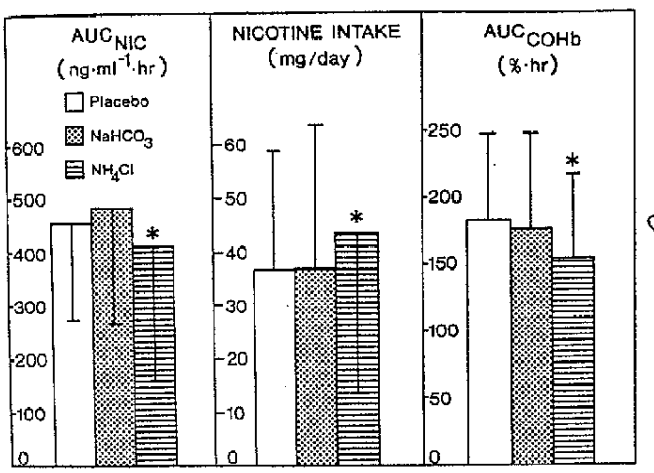

Fig. 2. Nicotine exposure [area under the blood nicotine concentration-time curve during 24 hr (AUC_{nic})] and intake and carbon monoxide exposure [area under the blood carboxyhemoglobin concentration-time curve during 24 hr (AUC_{COHb})] in placebo, alkaline ($NaHCO_3$) and acid (NH_4Cl) treatment conditions. *, significant differences, $NaHCO_3$ *vs.* NH_4Cl.

tine elimination rate and smoking behavior were modest. This is because renal excretion is a minor pathway for elimination of nicotine; most is metabolized. Smaller changes in urinary pH, such as occur spontaneously throughout the day or that might be related to stressful events, would not be expected to substantially influence nicotine elimination or smoking behavior. Alkali therapy has been advocated as a way to slow the rate of nicotine elimination and to reduce smoking (Fix *et al.*, 1983). Our data show that there is relatively little excretion of nicotine in base-line conditions (averaging 4 mg/day) and a decrease to 0.9 mg/day with alkali treatment has virtually no effect on body levels or smoking behavior. Thus, bicarbonate therapy would be expected to have little, if any, effect on cigarette consumption. This prediction is supported by other experimental studies (Cherek *et al.*, 1981).

In summary, we have shown that increasing the rate of elimination by acidification of the urine can increase nicotine consumption from cigarette smoking. As far as we know, this is the first direct demonstration that rate of elimination can influence drug consumption in humans.

Acknowledgments

The authors wish to thank Dr. Reese Jones for critical review of the manuscript, Gunnard Modin for statistical consultation, Chin Savanapridi for assistance in conducting clinical studies and performing nicotine analyses and Kaye Welch for preparing the manuscript.

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